BENZYNE AS AN INTERMEDIATE IN NUCLEOPHILIC AROMATIC SUBSTITUTION REACTIONS

By JOHN D. ROBERTS

(CALIFORNIA INSTITUTE OF TECHNOLOGY)

IT sometimes happens in organic chemistry that a large body of related fact accumulates which seemingly cannot be rationalized on the basis of the currently available theoretical concepts. In such circumstances, substantial clarification may often be achieved by an approach which is novel only in application to the system at hand. The pieces of the puzzle may then fall into place and experimental verification of predictions may be thereby achieved. However, it almost invariably occurs that the initial success is later tempered by experimental findings which either require modification of the original ideas or indicate their limitations.

In recent years, the interpretation of the rearrangements which sometimes occur in substitution reactions of non-activated aromatic halides with strong bases has gone through such a cycle. A rationalization of the pattern for this type of rearrangement was provided by postulation of an elimination–addition mechanism involving 'benzyne' intermediates[1] and there has been a rapid concomitant expansion of the chemistry of benzyne and related substances. At the same time, evidence has been accumulating that not all nucleophilic substitutions of non-activated aryl derivatives proceed by elimination–addition mechanisms.

Benzyne

It should be clearly evident that the concept of benzyne is

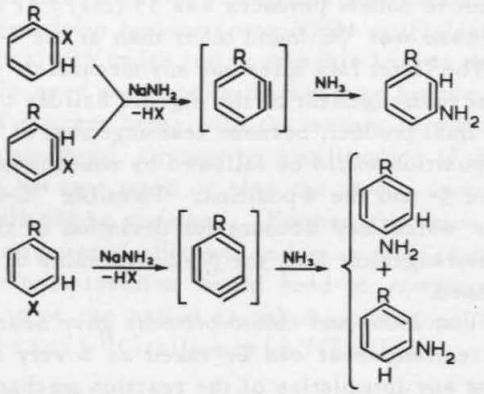
[1](*a*) Roberts, Simmons, jun., Carlsmith, and Vaughan, *J. Amer. Chem. Soc.*, 1953, **75**, 3290; (*b*) Roberts, Semenow, Simmons, jun., and Carlsmith, *ibid.*, 1956, **78**, 601.

not new. Indeed, names such as *o*-phenylenediamine which were coined in the early days of organic chemistry imply the existence of a molecule, *o*-phenylene C_6H_4, capable of undergoing addition reactions. Furthermore, formation of dodecahydrotriphenylene by trimerization of highly strained *cyclo*hexyne molecules was postulated by Favorsky and Boshowsky[2] in 1913 and a similar reaction path involving the *o*-phenylene diradical was suggested by Bachmann and Clark[3] for formation of triphenylene from *o*-dichlorobenzene and sodium. Elimination-addition mechanisms involving triply bonded intermediates were fully recognized by Reppe[4] in his studies of the reactions of vinyl chloride with alkoxides which give vinyl ethers. In addition, Wittig *et al.*[5] produced strong evidence for the formation of at least a virtual C_6H_4 intermediate in coupling reactions of aryl halides with organolithium compounds.

The early history of rearrangements during substitution of aromatic halides with strong bases has been well reviewed elsewhere.[6] It should suffice at this time to indicate the pattern of the results which is exemplified by the products of the various halogenoanisoles and halogenobenzotrifluorides with sodium amide in liquid ammonia or lithium diethylamide in diethyl ether. Even though the two substituent groups are considered to have opposite electrical effects as judged by their influence on orientation in aromatic nitration, these substances give essentially identical patterns of substitution products.[7-9] Thus, the *o*-halogeno-compounds give *meta*-amines, rearrangement being essentially quantitative. However, the *meta*-halides produce no detectable rearrangement products and the *para*-halides contrast with the others by giving roughly 1:1 mixtures of normal and rearranged products.

[2] Favorsky and Boshowsky, *Annalen*, 1912, **390**, 122.
[3] Bachmann and Clark, *J. Amer. Chem. Soc.*, 1927, **49**, 2089.
[4] Reppe, *G.P. 550,403* and *584,840*; *Chem. Abs.*, 1932, **26**, 4825; 1932, **28**, 1058.
[5] Wittig, Pieper, and Fuhrmann, *Ber.*, 1940, **73**, 1193; Wittig, *Naturwiss.*, 1942, **30**, 696.
[6] (*a*) Bunnett and Zahler, *Chem. Rev.*, 1951, **49**, 294; (*b*) Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell Univ. Press, Ithaca, N.Y., 1953, Chap. XV.
[7] Gilman and Avakian, *J. Amer. Chem. Soc.*, 1945, **67**, 349.
[8] Benkeser and Severson, *ibid.*, 1949, **71**, 3838.
[9] Roberts, Vaughan, Carlsmith, and Semenow, *ibid.*, 1956, **78**, 611.

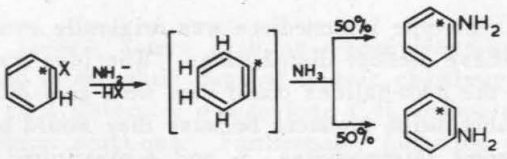
The benzyne-type intermediate was originally evoked to account for these product distributions. The idea was that the *ortho*- and the *para*-halides could very well give different patterns of substitution products because they would have to involve different intermediates, 3- and 4-substituted benzynes, respectively. Added to this were theoretical grounds[9] for expecting that organic halides with *m*-methoxy- or *m*-trifluoromethyl groups might yield only the corresponding 3-substituted benzynes and so would lead to the same products as the *ortho*-isomers by virtue of passing through a common intermediate.



Irrespective of its merits for rationalizing product distributions, this mechanism suggested a number of experiments. In the first place, for elimination of hydrogen halide, a hydrogen *ortho* to the halogen atom is clearly required. To test this point, some di-*o*-substituted aromatic halides were subjected to the action of alkali amide in liquid ammonia and of lithium diethylamide in ether under conditions where aryl halides having at least one *o*-hydrogen react readily. In no case was nucleophilic substitution on carbon observed, although with some compounds of this type there is attack on halogen to give reduction and other products.[10]

A more searching test of the elimination-addition mechanism was provided by recognition that it should lead to rearrangement with suitable isotopically labelled phenyl halides such as chloro[1-^{14}C]benzene. Indeed, if benzyne were formed, its sym-

[10] Benkeser and DeBoer, *J. Org. Chem.*, 1956,**21**,281,365.

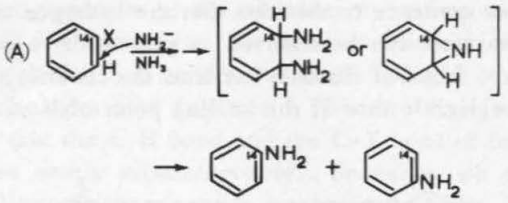


metry properties would be such as to predict formation of 50% of the normal and 50% of the rearranged product.

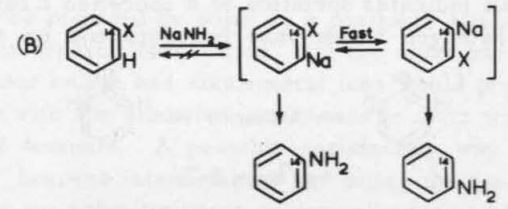
This prediction was confirmed by studying the extent of rearrangement in reactions of chloro- and iodo-[1-^{14}C]benzene with alkali amides in liquid ammonia.[1] In each case, the ratio of rearrangement to normal products was 53 (± 1) : 47 (± 1). Further, in no case was ^{14}C found other than at the 1- and the 2-position. The latter fact rules out any mechanism which might involve prior rearrangement of the organic halides or rearrangement of the final product, because rearrangement of ^{14}C from the 1- to the 2-position would be followed by subsequent rearrangements to the 3- and the 4-position. Possible ^{14}C-kinetic isotope effects which may account for deviation of the observed extent of rearrangement from the predicted value of 50·0% have been discussed.[1]

The fact that iodo- and chloro-benzene gave nearly identical extents of rearrangement can be taken as a very strong argument against any formulation of the reaction mechanism involving a fortuitous 1:1 mixture of normal and rearranging reactions. It would be very surprising indeed if the ratios of such reactions were the same for halides as different as chloro- and iodobenzene. None of these experiments 'proves' the benzyne mechanism but, at least, the results are not inconsistent with the operation of such a mechanism. It will be worthwhile at this point to consider other possible formulations which are in agreement with the evidence so far cited.

One possible mechanism[1b] which could account for the ^{14}C-experiment is an *addition–elimination* process involving either 1:2-diamino-1:2-dihydrobenzene or 'benzenimine', as shown in (A). Each of these intermediates has the correct symmetry properties to give a 1:1 mixture of normal and rearranged products. It is important to note that these intermediates must be formed by processes in which the hydrogen is removed after the halogen is removed. We shall return to this point below.



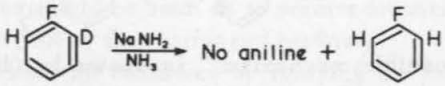
Another possible mechanism[1b] is shown by (B). Here, removal of hydrogen *ortho* to the halogen as a proton is postulated with amide ion acting as the base and, then, the resulting metallation product undergoes rapid halogen-equilibration so that the 1- and the 2-position become isotopically equivalent. Subsequent reactions with amide ion or ammonia lead to the aminated products. We need not specify mechanisms for the final step, our principal concern being with the manner in which the rearrangement is produced. Obviously, equilibration of the isomeric anions must be very rapid or else the proper amount of rearrangement will not be observed. Further, the anion cannot revert to starting material, if it is to undergo a rapid rearrangement, because the back-reaction would lead to rearranged halide. Rearrangement of the halide is ruled out because iodo[1-^{14}C]-benzene gives no [3-^{14}C]aniline or [4-^{14}C]aniline.



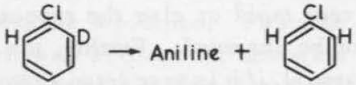
The relative merits of the above two mechanisms and the elimination–addition mechanism have been assessed by a detailed study[1b] of the role of the *o*-hydrogen atoms in the amination. With the aid of *o*-deutero-fluoro-, -chloro-, and -bromobenzene, the following facts were established. First, it was found that *o*-deuterofluorobenzene with amide in liquid ammonia gave no nucleophilic substitution but the *o*-deuterium was very rapidly exchanged by hydrogen from the ammonia.[11] In fact, exchange was found to be essentially complete in ten seconds. This ex-

[11] Hall, Piccolini, and Roberts, *J. Amer. Chem. Soc.*, 1955,77,4540.

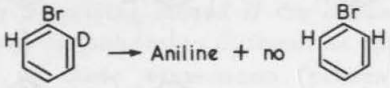
change gives credence to the idea that the hydrogen atoms *ortho* to a halogen atom can be removed as protons by a sufficiently strong base. Loss of fluoride ion from the resulting anion occurs at a negligible rate at the boiling point of liquid ammonia (−33°).



Secondly, *o*-chlorodeuterobenzene was found to undergo exchange and amination at comparable rates. Amination of *o*-chlorodeuterobenzene is thus shown to be a stepwise process in which the proton is removed by amide ion and the resulting ion either reverts to starting material with the gain of ordinary hydrogen from the ammonia or loses chloride ion to go on to give benzyne. Finally, with *o*-bromodeuterobenzene, only



amination was observed, there being no detectable exchange. Since overall amination rates for halogenobenzenes have been shown by Bergstrom *et al.*[12] to follow the order, F < Cl < Br > I, this result indicates operation of a concerted $E2$-type elimination of hydrogen halide from bromobenzene by amide ion.



$$k_H/k_D = 5{\cdot}7$$

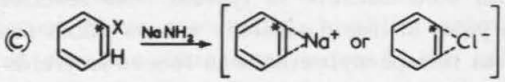
Further evidence that this is actually the case comes from the fact that the C–H bonds *ortho* to the bromine are broken by amide ion 5–6 times more rapidly than C–D bonds in the corresponding position. This primary H–D kinetic isotope effect is potent evidence for the breaking of the C–H bond in the rate-determining step, while the sequence of halogen reactivities mentioned above, F < Cl < Br > I, is similar direct evidence for the breaking of the C–X bond in the rate-determining step.

The results with deuterium-substituted halides may be used

[12] Bergstrom, Wright, Chandler, and Gilkey, *J. Org. Chem.*, 1936,**1**, 170.

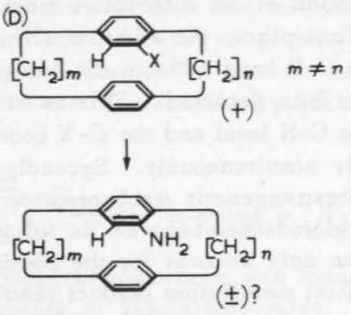
to rule out operation of the alternative mechanisms mentioned before. In the first place, the addition-elimination mechanism requires that the C-H bond *ortho* to the halogen be broken well *after* the halogen has departed. This is at variance with the evidence that the C-H bond and the C-X bond of bromobenzene are broken nearly simultaneously. Secondly, we can rule out the metallation-rearrangement mechanism on the basis of the behaviour of *o*-chlorodeuterobenzene as follows. Metallation-rearrangement can only account for the observed experimental results if the initial metallation product rearranges rapidly and does not revert to starting material. The experiments with *o*-chlorodeuterobenzene indicate that the initial metallation does in fact occur, but is reversible and leads to exchange of the *o*-deuterium. Therefore, since metallation occurs reversibly, the metallated intermediate cannot undergo rearrangement.

Two other kinds of intermediates are not ruled out by the experimental evidence now at hand. These are cationic and anionic complexes of benzyne, as shown in (C). These intermediates are not required by available experimental evidence

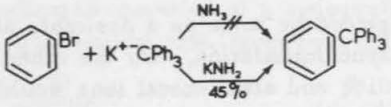


but might be regarded by some as a desirable alternative to an out-and-out benzyne formulation. On the other hand, it seems unlikely that halide and alkali-metal ions would prefer to form complexes with a hydrocarbon rather than to react with the large excess of ammonia. A possibly satisfactory way to find out how 'free' benzyne intermediates get during the reaction would be to carry out substitution on an optically active halide of the type shown in (D). It should be possible to make such a halide with such a number of methylene groups joining the rings so as to permit racemization of the corresponding benzyne intermediate *only* if it were stripped completely bare at the reactive positions.

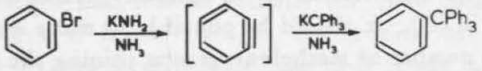
The distribution of rearrangement products obtained in the amination of substituted halogenobenzenes has been rationalized with the aid of the elimination-addition mechanism and various substituent influences of which the inductive effect seems most important.[9] The procedure is straightforward but too long to be presented here.



Competition experiments provide strong evidence for the belief that benzyne is a reasonably long-lived intermediate and also point the way to a number of novel and interesting synthetic reactions. The initial discoveries were made by Bergstrom and his co-workers[12,13] when they found that weak nucleophiles, which do not react with non-activated aromatic halides by themselves, can often be induced to do so in the presence of metal amides in liquid ammonia. The behaviour of sodium triphenylmethide with bromobenzene is typical. No reaction occurs at the boiling point of liquid ammonia unless alkali amide is present and then tetraphenylmethane is formed in yields up to 40%.

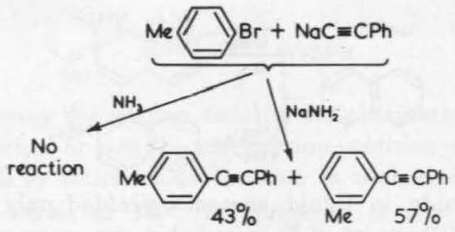


The reasonable interpretation of these reactions is that the amide ion activates the halogenobenzene by converting it into benzyne which then adds the weak nucleophilic agent to give



the final product. This interpretation is reinforced by the finding that such reactions customarily proceed with rearrangement and afford proportions of rearrangement products corresponding almost identically to those produced in other elimination–addi-

[13] Wright and Bergstrom, *ibid.*, **1936,1,179**; Seibert and Bergstrom, *ibid.*, **1945,10,544**; Bergstrom and Agostinho, *J. Amer. Chem. Soc.*, 1945,**67**,2152; Dirstine and Bergstrom, *J. Org. Chem.*, **1946,11,55**.

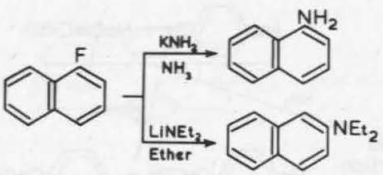


tion reactions.[14,15] The tendency for various substances to compete for benzyne with amide ion has been studied and found not to be easily correlated either with the electron-pair donating tendencies of the nucleophilic agent (as measured by proton affinities) or with reactivities toward alkyl halides.[14] In general, unsaturated nucleophiles are peculiarly effective. Thus, phenoxide is more effective than alkoxide, and anilide is comparable with amide. Interestingly, thiophenoxide is highly effective, giving diphenyl sulfide in yields up to 60% in competition with amide ion. This is particularly striking since there is a difference of some 25 powers of 10 between the base strengths of thiophenoxide and amide ions.

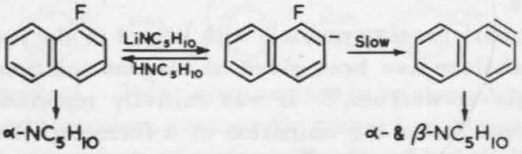
As mentioned above, not all nucleophilic substitutions of non-activated aromatic derivatives occur by the elimination-addition mechanisms. Examples of predominantly normal displacements include the cleavage of trimethylphenylammonium ions by sodium amide into aniline and trimethylamine,[1b] a variety of nucleophilic substitutions of compounds of diphenyliodonium type,[16] and the high-temperature aminolyses which do not utilize metal amides, studied by Bunnett *et al.*[17] Presumably, these reactions involve more or less normal S_N2 displacements.

A particularly vexing problem with regard to the amination of fluoronaphthalene has been given an elegant solution by Huisgen and his co-workers.[18] It was initially reported by Urner and Bergstrom[19] that the amination of α-fluoronaphthalene with

[14] Scardiglia and Roberts, *Tetrahedron*, in the press.
[15] Bunnett and Brotherton, *J. Org. Chem.*, in the press.
[16] Beringer, Brierly, Drexler, Gindler, and Lumpkin, *J. Amer. Chem. Soc.*, 1953,**75**,2708.
[17] Bunnett and Brotherton, *ibid.*, 1956,**78**,155,6265.
[18] Huisgen and Sauer, *Angew. Chem.*, 1957,**69**,390; Huisgen, Sauer, and Hauser, *ibid.*, p. 267.
[19] Urner and Bergstrom, *J. Amer. Chem. Soc.*, 1945,**67**,2108.

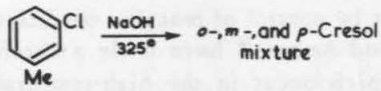


potassium amide in liquid ammonia yielded only α-naphthylamine while Gilman *et al.*[20] stated that the same substance reacted with lithium diethylamide in ether to give only the β-isomer. This behaviour is particularly puzzling because in no other case has a difference been reported between the general types of isomer distributions obtained with these reagents. In Huisgen's work, it was found that the amination of α-fluoronaphthalene with lithium piperidide gave mixtures the composition of which depended on the piperidine concentration – the more piperidine, the less rearrangement. This behaviour can be interpreted in terms of an equilibrium proton-transfer involving α-fluoronaphthalene and lithium piperidide to give the 1-fluoro-2-naphthyl anion. This anion can either gain a proton from piperidine and be reconverted into α-fluoronaphthalene or lose fluoride ion to give naphthalyne and thence go on to rearrangement products. If α-fluoronaphthalene is capable of also undergoing a slow direct reaction with lithium piperidide to give α-naphthylpiperidine, then the dependence of the degree of rearrangement on the concentration of piperidine is the consequence of a mass-action lowering of the fluoro-anion concentration by piperidine acting as an acid. With sodium amide in liquid ammonia, the large excess of ammonia keeps the anion concentration low and favours direct attack at the α-position.

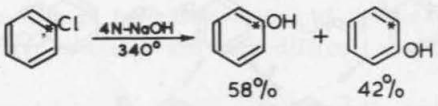


The high-temperature alkaline hydrolysis of aryl chlorides to phenols has the appearance of a benzyne-type reaction in that the chlorotoluenes react with rearrangement to give product dis-

[20] Gilman, Crounse, Massie, Jun., Benkeser, and Spatz, *ibid.*, p. 2106.



tributions having the pattern familiar for elimination–addition.[21] To test whether or not the elimination–addition mechanism is the sole path by which chlorobenzene is converted into phenol by aqueous alkali at 340°, the products of the hydrolysis of chloro[1-^{14}C]benzene were investigated.[22] [1-^{14}C]Phenol and [2-^{14}C]phenol were found to be formed in the ratio of 58:42 in place of the 50:50 split predicted if benzyne were the exclusive intermediate. Obviously, this result indicates more than one



mechanism for the high-temperature hydrolysis of aryl halides and therefore an extensive study was made, with halogenotoluenes, of the factors which determine the balance between the mechanisms.[22] The pattern of experimental results is shown in the Table. It will be seen that the degree of rearrangement is

Products from the hydrolysis of p-*halogenotoluenes at elevated temperatures:*

p-Me·$C_6H_4X \rightarrow$ p- + m-Me·C_6H_4·OH

X	Temp.	Base	*para*(%)	*meta*(%)
Cl	340°	1–8N-NaOH	50	50
Cl	340	4N-NaOAc	90	10
Br	340	N-NaOH	50	50
Br	340	4N-NaOAc	100	0
Br	250	N-NaOH	78	22
I	250	N-NaOH	97	3

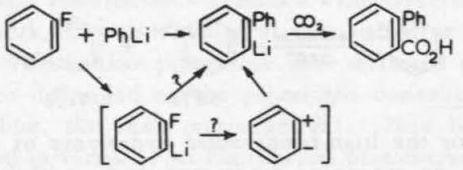
generally a proper function of those variables which regularly influence the ratio of elimination to direct substitution for alkyl halides.[23] Thus, elimination–addition by way of benzyne-type intermediates is favoured by increasing temperature, increasing base strength of reagent, and in the order Cl > Br > I for the several halides. These findings permit effective control over

[21] Shreve and Marsel, *Ind. Eng. Chem.*, 1946,**38**,254.
[22] Bottini and Roberts, *J. Amer. Chem. Soc.*, 1957,**79**,1458.
[23] Ref. 6*b*, Chap. VI and VII.

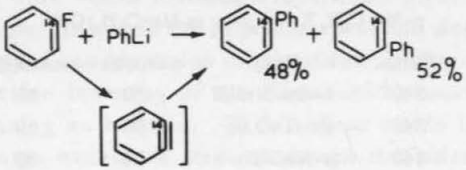
the rearrangement by control of reaction conditions.

Lüttringhaus and Ambros[24] have made a careful study of the side-reactions which occur in the high-temperature hydrolysis of chlorobenzene with concentrated alkali and have shown how the resulting products can be rationalized on the basis of the benzyne intermediate.

It was postulated by Wittig[5,25] that the coupling of fluorobenzene with phenyl-lithium proceeded by way of either a dipolar ion of formula C_6H_4 or *o*-lithiofluorobenzene because the reaction product was *o*-lithiodiphenyl, which was not obtainable by metallation of diphenyl with phenyl-lithium. Experiments with

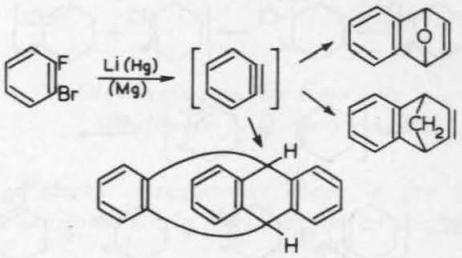


fluoro[1-^{14}C]benzene have shown that this reaction proceeds by way of a symmetrical intermediate and that approximately equal quantities of [1-^{14}C]- and [2-^{14}C]-diphenyl are formed.[26] Similar conclusions have been reached by Huisgen and Rist[27] in studies of the coupling of fluoronaphthalenes with phenyl-lithium.



No work on the discussion of benzyne as a reaction intermediate would be complete without reference to the extraordinary studies by Wittig and his co-workers[28] on Diels-Alder addition reactions. Starting with *o*-bromofluorobenzene and metals such as magnesium or lithium amalgam, Wittig has been

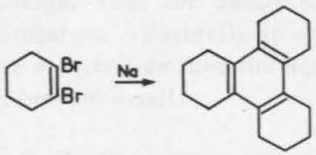
[24] Lüttringhaus and Ambros, *Chem. Ber.*, 1956,**89**,463.
[25] Wittig, *Angew. Chem.*, 1954,**66**,10.
[26] Jenny and Roberts, *Helv. Chim. Acta*, 1955,**38**,1248.
[27] Huisgen and Rist, *Naturwiss.*, 1954,**41**,358; *Annalen*, 1955,**594**, 127.
[28] Wittig and Pohmer, *Angew. Chem.*, 1955,**67**,348; *Chem. Ber.*, **1956,89,1334**; Wittig and Ludwig, *Angew. Chem.*, 1956,**68**,40; Wittig, *ibid.*, 1957,**69**,245.



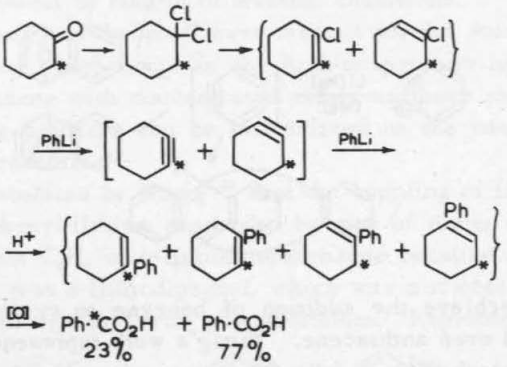
able to achieve the addition of benzyne to *cyclo*pentadiene, furan, and even anthracene. Wittig's work represents an extraordinary break-through for achievement of syntheses of benzo-derivatives of types which are very difficult to obtain by other means.

The successful application of the elimination-addition mechanism to substitution of non-activated aromatic halides suggests the possibility that vinyl halides in general may function similarly. Evidence that this is the case is provided by the aforementioned discovery by Reppe[4] that vinyl chloride is converted into ethyl vinyl ether by sodium ethoxide in ethanol through acetylene as an intermediate, and also by recent studies of nucleophilic substitution of dihalogenoethylenes by Truce *et al.*[29]

Special interest is attached to the reactions of those vinyl halides which would give highly strained acetylenic intermediates which, like benzyne, might not be isolable under ordinary conditions. *cyclo*Hexyne is suggested as a reasonable candidate for a first step in this direction by the reported formation of dodecahydrotriphenylene from 1:2-dibromo*cyclo*hexene and sodium,[2] and it has recently been shown that coupling phenyl-lithium with ^{14}C-labelled chloro*cyclo*hexene affords 1-phenyl*cyclo*hexene by way of an intermediate possessing the



[29] Truce, Boudakian, Heine, and McManimie, *J. Amer. Chem. Soc.*, 1956,78,2743; Truce and Boudakian, *ibid.*, pp. 2748,2752.



symmetry properties of *cyclo*hexyne.[30] Further studies of this variety are in progress.

The scope, limitations, and utility of the benzyne mechanism in accounting for the products of the reactions of vinyl and aryl halides with strongly basic reagents are now becoming much clearer. There can be little question that the results so far obtained point the way toward a measure of control over the rearrangement and, in addition, have aided in the development of new synthetic procedures for interesting and difficultly attainable substances.

[30] Scardiglia and Roberts, *Tetrahedron*, 1957,1,343.

Discussion on the Paper by
Professor J. D. Roberts

Dr. V. A. Petrow. Presumably there is the possibility of reducing the steric strain in *cyclo*hexyne by increasing the ring size.

Professor J. D. Roberts. Larger-ring *cyclo*alkynes have been reported. It is my impression that *cyclo*octyne is reasonably stable.

Dr. D. H. Reid. What is the state of the two electrons which you have represented formally as the third part of the triple bond in the benzyne molecule?

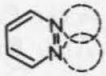
Professor J. D. Roberts. This is a very reasonable question but I do not know the answer.

I was surprised by Coulson's result given this morning in which he calculates a high degree of triple-bond character for this bond. The extra bond may range in character from no bond (as expected for a triplet state) all the way to a rather tight triple bond as predicted by Professor Coulson.

This much is true. Benzyne appears to be exceedingly reactive, as in its reaction with anthracene which is certainly very inert in other Diels–Alder reactions. The large reactivity of benzyne is also apparent from the seemingly incoherent orders of reactivity towards various nucleophiles. The only apparent reactivity factor which appears to make sense is the possible degree of solvation of the nucleophile at the reactive site. The unsaturated nucleophiles may be particularly effective in competition because they are more lightly solvated, owing to their dispersed charge, than the saturated nucleophiles with their concentrated charge. Naturally if solvation alone determines their relative reactivities then the activation energies for the reactions must be very small.

Professor M. J. S. Dewar. There is quite a high degree of orbital overlap in the benzyne molecule.

Dr. S. F. Mason. A stable hetero-aromatic analogue of the benzyne dianion is the *o*-diazine, pyridazine (I). Here the calculated overlap, on the basis of Slater orbitals, of the lone-pair



(I)

nitrogen sp^2-orbitals is $\sim 0{\cdot}1$, so that there must be considerable interaction between them. The interaction splits the lone-pair levels, one becoming more bonding and the other becoming less bonding. The splitting is shown in the case of pyridazine by the position of the $n \rightarrow \pi$ transition, which lies at a longer wavelength than for the isomers, pyrimidine and pyrazine. In pyridazine, both of the split levels must be occupied, but in the benzyne molecule only the lower, more bonding level is occupied. Thus in-plane π-type overlap of the singly occupied sp^2-orbitals may result in a considerable stabilisation of the benzyne intermediate.

Professor J. D. Roberts. The attack of nucleophilic reagents on substituted benzynes indicates that the π-electrons of the benzene ring are not involved, since with either *ortho-*, *meta-*, or *para*-directing substituents at the 3-position attack still occurs at the 1- position. Presumably nucleophilic reagents come up to attack the carbon atom in position 1 in the plane of the aromatic ring.